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  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:56:01 ON 17 DEC 2004

=> fil .bec
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       1.47       1.47

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 14:59:57 ON 17 DEC 2004
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11 FILES IN THE FILE LIST

=> s ikk?
FILE 'MEDLINE'
L1         2120 IKK?

FILE 'SCISEARCH'
L2         1332 IKK?

FILE 'LIFESCI'
L3          518 IKK?

FILE 'BIOTECHDS'
L4           57 IKK?

FILE 'BIOSIS'
L5         1199 IKK?

FILE 'EMBASE'
L6          949 IKK?

FILE 'HCAPLUS'
L7         1282 IKK?

FILE 'NTIS'
L8           44 IKK?

FILE 'ESBIOBASE'
L9          841 IKK?

FILE 'BIOTECHNO'
L10         490 IKK?

FILE 'WPIDS'
L11         133 IKK?

TOTAL FOR ALL FILES
L12        8965 IKK?

=> s l12(5a)complex?
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L13        273 L1 (5A)COMPLEX?

FILE 'SCISEARCH'
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L14        298 L2 (5A)COMPLEX?

FILE 'LIFESCI'
        182403 COMPLEX?
L15        174 L3 (5A)COMPLEX?
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FILE 'BIOTECHDS'
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L18       260 L6 (5A)COMPLEX?

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L19       299 L7 (5A)COMPLEX?

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L20         6 L8 (5A)COMPLEX?

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       206585 COMPLEX?
L21       242 L9 (5A)COMPLEX?

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L22       171 L10(5A)COMPLEX?

FILE 'WPIDS'
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L23        10 L11(5A)COMPLEX?

TOTAL FOR ALL FILES
L24      2024 L12(5A) COMPLEX?

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FILE 'MEDLINE'
       878701 EXPRESS?
        12184 COEXPRESS?
L25        19 L13(15A)(EXPRESS? OR COEXPRESS?)

FILE 'SCISEARCH'
      1119416 EXPRESS?
        12490 COEXPRESS?
L26        30 L14(15A)(EXPRESS? OR COEXPRESS?)

FILE 'LIFESCI'
       358622 EXPRESS?
         5643 COEXPRESS?
L27        15 L15(15A)(EXPRESS? OR COEXPRESS?)

FILE 'BIOTECHDS'
       120713 EXPRESS?
          557 COEXPRESS?
L28         2 L16(15A)(EXPRESS? OR COEXPRESS?)

FILE 'BIOSIS'
      1058238 EXPRESS?
        12323 COEXPRESS?
L29        20 L17(15A)(EXPRESS? OR COEXPRESS?)

FILE 'EMBASE'
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L30        27 L18(15A)(EXPRESS? OR COEXPRESS?)

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       1075138 EXPRESS?
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L31         19 L19(15A)(EXPRESS? OR COEXPRESS?)

FILE 'NTIS'
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L32          3 L20(15A)(EXPRESS? OR COEXPRESS?)

FILE 'ESBIOBASE'
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L33         26 L21(15A)(EXPRESS? OR COEXPRESS?)

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          7587 COEXPRESS?
L34         17 L22(15A)(EXPRESS? OR COEXPRESS?)

FILE 'WPIDS'
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           130 COEXPRESS?
L35          3 L23(15A)(EXPRESS? OR COEXPRESS?)

TOTAL FOR ALL FILES
L36        181 L24(15A)(EXPRESS? OR COEXPRESS?)

=> s l36 not 2002-2004/py
FILE 'MEDLINE'
       1631836 2002-2004/PY
L37          9 L25 NOT 2002-2004/PY

FILE 'SCISEARCH'
       2992695 2002-2004/PY
L38         12 L26 NOT 2002-2004/PY

FILE 'LIFESCI'
        278729 2002-2004/PY
L39          9 L27 NOT 2002-2004/PY

FILE 'BIOTECHDS'
         68835 2002-2004/PY
L40          0 L28 NOT 2002-2004/PY

FILE 'BIOSIS'
       1445602 2002-2004/PY
L41         10 L29 NOT 2002-2004/PY

FILE 'EMBASE'
       1405485 2002-2004/PY
L42         12 L30 NOT 2002-2004/PY

FILE 'HCAPLUS'
       3121692 2002-2004/PY
L43          9 L31 NOT 2002-2004/PY

FILE 'NTIS'
         35422 2002-2004/PY
L44          1 L32 NOT 2002-2004/PY
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FILE 'ESBIOBASE'
        848800 2002-2004/PY
L45          12 L33 NOT 2002-2004/PY

FILE 'BIOTECHNO'
        244553 2002-2004/PY
L46          10 L34 NOT 2002-2004/PY

FILE 'WPIDS'
       3017627 2002-2004/PY
L47           0 L35 NOT 2002-2004/PY

TOTAL FOR ALL FILES
L48          84 L36 NOT 2002-2004/PY

=> dup rem l48
PROCESSING COMPLETED FOR L48
L49           17 DUP REM L48 (67 DUPLICATES REMOVED)

=> d tot

L49  ANSWER 1 OF 17      MEDLINE on STN                    DUPLICATE 1
TI   Tumor necrosis factor (TNF) and phorbol ester induce TNF-related
     apoptosis-inducing ligand (TRAIL) under critical involvement of NF-kappa B
     essential modulator (NEMO)/IKKgamma.
SO   Journal of biological chemistry, (2001 Nov 23) 276 (47) 43708-12.
     Journal code: 2985121R. ISSN: 0021-9258.
AU   Siegmund D; Hausser A; Peters N; Scheurich P; Wajant H
AN   2001667620      MEDLINE

L49  ANSWER 2 OF 17      MEDLINE on STN                    DUPLICATE 2
TI   Complete reconstitution of human IkappaB kinase (IKK) complex in yeast.
     Assessment of its stoichiometry and the role of IKKgamma on the complex
     activity in the absence of stimulation.
SO   Journal of biological chemistry, (2001 Sep 28) 276 (39) 36320-6.
     Journal code: 2985121R. ISSN: 0021-9258.
AU   Miller B S; Zandi E
AN   2001522209      MEDLINE

L49  ANSWER 3 OF 17  SCISEARCH  COPYRIGHT (c) 2004 The Thomson Corporation.  on
     STN                                                DUPLICATE 3
TI   The PTEN tumor suppressor protein inhibits tumor necrosis factor-induced
     nuclear factor kappa B activity
SO   JOURNAL OF BIOLOGICAL CHEMISTRY, (20 JUL 2001) Vol. 276, No. 29, pp.
     27740-27744.
     Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE
     PIKE, BETHESDA, MD 20814 USA.
     ISSN: 0021-9258.
AU   Gustin J A; Maehama T; Dixon J E; Donner D B (Reprint)
AN   2001:582569  SCISEARCH

L49  ANSWER 4 OF 17      MEDLINE on STN                    DUPLICATE 4
TI   Novel NEMO/IkappaB kinase and NF-kappa B target genes at the pre-B to
     immature B cell transition.
SO   Journal of biological chemistry, (2001 May 25) 276 (21) 18579-90.
     Journal code: 2985121R. ISSN: 0021-9258.
AU   Li J; Peet G W; Balzarano D; Li X; Massa P; Barton R W; Marcu K B
AN   2001316128      MEDLINE

L49  ANSWER 5 OF 17      MEDLINE on STN                    DUPLICATE 5
TI   Inhibition of the nuclear factor kappa B (NF-kappa B) pathway by
     tetracyclic kaurene diterpenes in macrophages. Specific effects on
     NF-kappa B-inducing kinase activity and on the coordinate activation of
     ERK and p38 MAPK.
```

SO Journal of biological chemistry, (2001 May 11) 276 (19) 15854-60.
Journal code: 2985121R. ISSN: 0021-9258.
AU Castrillo A; de Las Heras B; Hortelano S; Rodriguez B; Villar A; Bosca L
AN 2001291007 MEDLINE

L49 ANSWER 6 OF 17 MEDLINE on STN DUPLICATE 6
TI Role of IKKgamma/nemo in assembly of the Ikappa B kinase complex.
SO Journal of biological chemistry, (2001 Feb 9) 276 (6) 4494-500.
Journal code: 2985121R. ISSN: 0021-9258.
AU Li X H; Fang X; Gaynor R B
AN 2001268720 MEDLINE

L49 ANSWER 7 OF 17 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 7
TI Conjugated polyhydroxybenzene derivatives block tumor necrosis factor-alpha-mediated nuclear factor-kappa B activation and cyclooxygenase-2 gene transcription by targeting I kappa B kinase activity
SO MOLECULAR PHARMACOLOGY, (DEC 2001) Vol. 60, No. 6, pp. 1439-1448.
Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
ISSN: 0026-895X.
AU Chen C C (Reprint); Chiu K T; Chan S T; Chern J W
AN 2001:996044 SCISEARCH

L49 ANSWER 8 OF 17 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
TI CD40 signaling in B cells regulates the expression of pim-1 via the NF-kappaB pathway.
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A703. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
AU Zhu, Mindy [Reprint author]; Ramirez, Luis; Lee, Rosaline [Reprint author]; Pelech, Steve; Bishop, Gail; Gold, Michael [Reprint author]
AN 2001:276736 BIOSIS

L49 ANSWER 9 OF 17 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
TI Activation of NF-kappaB by hepatitis B virus X protein through an IkappaB kinase-independent mechanism.
SO American Journal of Physiology, (April, 2001) Vol. 280, No. 4 Part 1, pp. G669-G677. print.
CODEN: AJPHAP. ISSN: 0002-9513.
AU Purcell, Nicole H.; Yu, Chenfei; He, Daoyao; Xiang, Jialing; Paran, Nir; DiDonato, Joseph A.; Yamaoka, Shoji; Shaul, Yosef; Lin, Anning [Reprint author]
AN 2001:313341 BIOSIS

L49 ANSWER 10 OF 17 MEDLINE on STN DUPLICATE 8
TI S phase dependence and involvement of NF-kappaB activating kinase to NF-kappaB activation by camptothecin.
SO Biochemical pharmacology, (2001 Sep 1) 62 (5) 603-16.
Journal code: 0101032. ISSN: 0006-2952.
AU Habraken Y; Piret B; Piette J
AN 2001537538 MEDLINE

L49 ANSWER 11 OF 17 NTIS COPYRIGHT 2004 NTIS on STN
TI Characterization of a B-Catenin-Associated Kinase. Annual rept. 1 Aug 1999-31 Jul 2000.
NR ADA389329/XAB
20p; Aug 2000
PD Aug 2000
AU Byers, S.; Orford, K.

AN 2001(16):06687 NTIS

L49 ANSWER 12 OF 17 MEDLINE on STN DUPLICATE 9
TI Selective inhibition of NF-kappaB activation by a peptide that blocks the interaction of NEMO with the IkappaB kinase complex.
SO Science, (2000 Sep 1) 289 (5484) 1550-4.
Journal code: 0404511. ISSN: 0036-8075.
AU May M J; D'Acquisto F; Madge L A; Glockner J; Pober J S; Ghosh S
AN 2000431571 MEDLINE

L49 ANSWER 13 OF 17 MEDLINE on STN DUPLICATE 10
TI Somatic mutagenesis studies of NF-kappa B signaling in human T cells: evidence for an essential role of IKK gamma in NF-kappa B activation by T-cell costimulatory signals and HTLV-I Tax protein.
SO Oncogene, (2000 Mar 9) 19 (11) 1448-56.
Journal code: 8711562. ISSN: 0950-9232.
AU Harhaj E W; Good L; Xiao G; Uhlik M; Cvijic M E; Rivera-Walsh I; Sun S C
AN 2000190098 MEDLINE

L49 ANSWER 14 OF 17 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 11
TI NF-kappa B activation by double-stranded-RNA-activated protein kinase (PKR) is mediated through NF-kappa B-inducing kinase and I kappa B kinase
SO MOLECULAR AND CELLULAR BIOLOGY, (FEB 2000) Vol. 20, No. 4, pp. 1278-1290.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0270-7306.
AU ZamanianDaryoush M; Mogensen T H; DiDonato J A; Williams B R G (Reprint)
AN 2000:99608 SCISEARCH

L49 ANSWER 15 OF 17 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 12
TI The human T-cell leukemia virus type-1 Tax protein regulates the activity of the I kappa B kinase complex
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (26 NOV 1999) Vol. 274, No. 48, pp. 34417-34424.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
AU Li X H; Murphy K M; Palka K T; Surabhi R M; Gaynor R B (Reprint)
AN 1999:921944 SCISEARCH

L49 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-κB activation via the NIK/IKK signalling complex
SO Oncogene (1999), 18(44), 6013-6020
CODEN: ONCNES; ISSN: 0950-9232
AU Plummer, Simon M.; Holloway, Karen A.; Manson, Margaret M.; Munks, Rebecca J. L.; Kaptein, Allard; Farrow, Stuart; Howells, Lynne
AN 1999:735171 HCAPLUS
DN 132:44613

L49 ANSWER 17 OF 17 MEDLINE on STN DUPLICATE 13
TI Primary human CD4+ T cells contain heterogeneous I kappa B kinase complexes: role in activation of the IL-2 promoter.
SO Journal of immunology (Baltimore, Md. : 1950), (1999 Nov 15) 163 (10) 5444-52.
Journal code: 2985117R. ISSN: 0022-1767.
AU Khoshnan A; Kempiak S J; Bennett B L; Bae D; Xu W; Manning A M; June C H; Nel A E
AN 2000021841 MEDLINE

=> d ab tot

L49 ANSWER 1 OF 17 MEDLINE on STN DUPLICATE 1
AB We show that tumor necrosis factor (TNF) and phorbol 12-myristate 13-acetate (PMA) induce TNF-related apoptosis-inducing ligand (TRAIL) in T cells. In cells deficient for NF-kappaB essential modulator (NEMO)/IKKgamma, an essential component of the NF-kappaB-inducing I-kappaB kinase (**IKK**) **complex**, induction of TRAIL **expression** was completely abrogated but was recovered in cells restored for IKKgamma **expression.** In cells deficient for receptor-interacting protein expression TNF, but not PMA-induced TRAIL expression was blocked. Inhibition of protein synthesis with cycloheximide blocked PMA, but not TNF-induced up-regulation of TRAIL. As both TNF and PMA rapidly induce NF-kappaB activation this suggests that NEMO/IKKgamma-dependent activation of the NF-kappaB pathway is necessary but not sufficient for up-regulation of TRAIL in T cells. The capability of the NF-kappaB pathway to induce the potent death ligand TRAIL may explain the reported proapoptotic features of this typically antiapoptotic pathway.

L49 ANSWER 2 OF 17 MEDLINE on STN DUPLICATE 2
AB The IkappaB kinase (IKK) complex, composed of two catalytic subunits (IKKalpha and IKKbeta) and a regulatory subunit (IKKgamma), is the key enzyme in activation of nuclear factor kappaB (NF-kappaB). To study the mechanism and structure of the **complex**, we wanted to recombinantly **express IKK** in a model organism that lacks IKK. For this purpose, we have recombinantly reconstituted all three subunits together in yeast and have found that it is biochemically similar to IKK isolated from human cells. We show that there is one regulatory subunit per kinase subunit. Thus, the core subunit composition of IKKalphaβgamma complex is alpha(1)beta(1)gamma(2), and the core subunit composition of IKKbeta.gamma is beta(2)gamma(2). The activity of the **IKK complex** (alpha+beta+gamma or beta+gamma) **expressed** in yeast (which lack NF-kappaB and IKK) is 4-5-fold higher than an equivalent amount of IKK from nonstimulated HeLa cells. In the absence of IKKgamma, IKKbeta shows a level of activity similar to that of IKK from nonstimulated HeLa cells. Thus, IKKgamma activates IKK complex in the absence of upstream stimuli. Deleting the gamma binding domain of IKKbeta or IKKalpha prevented IKKgamma induced activation of IKK complex in yeast, but it did not prevent the incorporation of IKKgamma into IKK and large complex formation. The possibility of IKK complex being under negative control in mammalian cells is discussed.

L49 ANSWER 3 OF 17 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 3
AB Nuclear factor kappaB (NF-kappaB) transcriptionally activates genes that promote immunity and cell survival. Activation of NF-kappaB is induced by an I kappaB kinase (IKK) complex that phosphorylates and promotes dissociation of I kappaB from NF-kappaB, which then translocates into the nucleus. Activation of phosphatidylinositol (PI) 3-kinase/Akt signaling by tumor necrosis factor (TNF) activates IKK and NF-kappaB. The present study shows that PTEN, a tumor suppressor that inhibits PI 3-kinase function, impairs TNF activation of Akt and the **IKK complex** in 293 cells. Transient **expression** of PTEN suppressed IKK activation and TNF-induced NF-kappaB DNA binding and transactivation. Studies were conducted with PC-3 prostate cancer cells that do not express PTEN and DU145 prostate cancer cells that express PTEN. TNF activated Akt in PC-3 cells, but not in DU145 cells, and the ability of TNF to activate NF-kappaB was blocked by pharmacological inhibition of PI 3-kinase activity in PC-3 cells, but not in DU145 cells. Expression of PTEN in PC-3 cells to a level comparable with that endogenously present in DU145 cells inhibited TNF activation of NF-kappaB. The cell type-specific ability of PTEN to negatively regulate the PI 3-kinase/AKT/NF-kappaB pathway may be important to its tumor suppressor

activity.

L49 ANSWER 4 OF 17 MEDLINE on STN DUPLICATE 4
AB The IkappaB kinase (**IKK**) signaling **complex** is responsible for activating NF-kappaB-dependent gene **expression** programs. Even though NF-kappaB-responsive genes are known to orchestrate stress-like responses, critical gaps in our knowledge remain about the global effects of NF-kappaB activation on cellular physiology. DNA microarrays were used to compare gene expression programs in a model system of 70Z/3 murine pre-B cells versus their IKK signaling-defective 1.3E2 variant with lipopolysaccharide (LPS), interleukin-1 (IL-1), or a combination of LPS + phorbol 12-myristate 13-acetate under brief (2 h) or long term (12 h) stimulation. 70Z/3-1.3E2 cells lack **expression** of NEMO/IKKgamma/IKKAP-1/FIP-3, an essential positive effector of the **IKK complex.** Some stimulated hits were known NF-kappaB target genes, but remarkably, the vast majority of the up-modulated genes and an unexpected class of repressed genes were all novel targets of this signaling pathway, encoding transcription factors, receptors, extracellular ligands, and intracellular signaling factors. Thirteen stimulated (B-ATF, Pim-2, MyD118, Pea-15/MAT1, CD82, CD40L, Wnt10a, Notch 1, R-ras, Rgs-16, PAC-1, ISG15, and CD36) and five repressed (CCR2, VpreB, lambda5, SLPI, and CMAP/Cystatin7) genes, respectively, were bona fide NF-kappaB targets by virtue of their response to a transdominant IkappaBalphaSR (super repressor). MyD118 and ISG15, although directly induced by LPS stimulation, were unaffected by IL-1, revealing the existence of direct NF-kappaB target genes, which are not co-induced by the LPS and IL-1 Toll-like receptors.

L49 ANSWER 5 OF 17 MEDLINE on STN DUPLICATE 5
AB The anti-inflammatory action of most terpenes has been explained in terms of the inhibition of nuclear factor kappaB (NF-kappaB) activity. Ent-kaurene diterpenes are intermediates of the synthesis of gibberellins and inhibit the expression of NO synthase-2 and the release of tumor necrosis factor-alpha in J774 macrophages challenged with lipopolysaccharide. These diterpenes inhibit NF-kappaB and IkappaB kinase (IKK) activation in vivo but failed to affect in vitro the function of NF-kappaB, the phosphorylation and targeting of IkappaBalpha, and the activity of IKK-2. Transient **expression** of NF-kappaB-inducing kinase (NIK) activated the **IKK complex** and NF-kappaB, a process that was inhibited by kaurenes, indicating that the inhibition of NIK was one of the targets of these diterpenes. These results show that kaurenes impair the inflammatory signaling by inhibiting NIK, a member of the MAPK kinase superfamily that interacts with tumor necrosis factor receptor-associated factors, and mediate the activation of NF-kappaB by these receptors. Moreover, kaurenes delayed the phosphorylation of p38, ERK1, and ERK2 MAPKs, but not that of JNK, in response to lipopolysaccharide treatment of J774 cells. The absence of a coordinate activation of MAPK and IKK might contribute to a deficient activation of NF-kappaB that is involved in the anti-inflammatory activity of these molecules.

L49 ANSWER 6 OF 17 MEDLINE on STN DUPLICATE 6
AB IKKgamma/NEMO is a protein that is critical for the assembly of the high molecular weight IkappaB kinase (IKK) complex. To investigate the role of IKKgamma/NEMO in the assembly of the IKK complex, we conducted a series of experiments in which the chromatographic distribution of extracts prepared from cells transiently expressing epitope-tagged IKKgamma/NEMO and the IKKs were examined. When expressed alone following transfection, IKKalpha and IKKbeta were present in low molecular weight complexes migrating between 200 and 400 kDa. However, when coexpressed with IKKgamma/NEMO, both IKKalpha and IKKbeta migrated at approximately 600 kDa which was similar to the previously described IKK complex that is activated by cytokines such as tumor necrosis factor-alpha. When either IKKalpha or IKKbeta was **expressed** alone with IKKgamma/NEMO, IKKbeta but not

IKKalpha migrated in the higher molecular weight **IKK complex.** Constitutively active or inactive forms of IKKbeta were both incorporated into the high molecular weight IKK complex in the presence of IKKgamma/NEMO. The amino-terminal region of IKKgamma/NEMO, which interacts directly with IKKbeta, was required for formation of the high molecular weight IKK complex and for stimulation of IKKbeta kinase activity. These results suggest that recruitment of the IKKs into a high molecular complex by IKKgamma/NEMO is a crucial step involved in IKK function.

L49 ANSWER 7 OF 17 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 7

AB Because the transcription factor, nuclear factor (NF)-kappaB, plays a key role in cellular inflammatory and immune responses, components of the NF-kappaB-activating signaling pathways are frequently used as targets for anti-inflammatory agents. This study shows that 2-(3'4'-dihydroxyphenyl)-5-hydroxybenzo[b]furan (GF-015) and 2,3-di(3'4'-dihydroxy-transstyryl) pyridine (GF-90), two conjugated polyhydroxybenzene derivatives, inhibited a common step in NF-kappaB activation in human NCl-H292 epithelial cells by preventing tumor necrosis factor (TNF)-alpha- and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced I kappaB kinase (**IKK**) **complex** activation. Both agents inhibited the TNF-alpha- or TPA-induced **expression** of cyclooxygenase (COX)-2 mRNA and protein, COX-2 promoter activity, and prostaglandin E-2 (PGE(2)) production. Overexpression of wild-type NF-kappaB-inducing kinase, IKK alpha, and IKK beta led, respectively, to 3.5-, 2.6-, and 2.6-fold increases in COX-2 promoter activity, and these effects were inhibited by both compounds. GF-015 and GF-90 also prevented the TNF-alpha- and TPA-induced activation of IKK and NF-kappaB-specific DNA-protein binding activity. These results suggest that the inhibitory effect of GF-015 and GF-90 on TNF-alpha -induced COX-2 protein expression was caused by suppression of IKK activity and NF-kappaB activation in the COX-2 promoter, resulting in attenuation of COX-2 gene expression and PGE(2) production.

L49 ANSWER 8 OF 17 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

AB CD40 signaling plays an important role in B cell growth, survival, differentiation and Ig isotype class switching. These effects are likely to involve changes in the expression of a number of genes. Using cDNA expression arrays, we found that CD40 signaling increased the expression of pim-1, a proto-oncogene that encodes a serine/threonine kinase. Northern blotting showed that CD40-induced increases in pim-1 mRNA levels could be detected within 30 min in both the WEHI-231 and M12 B cell lines. CD40 signaling also caused a significant increase in the levels of the Pim-1 protein in both the cytoplasm and nucleus of WEHI-231 cells, M12 cells and murine splenic B cells. In addition, we showed that the CD40-induced increases in pim-1 mRNA levels were not blocked by the protein synthesis inhibitor cycloheximide. This indicates that up-regulation of pim-1 expression is an early and primary event in CD40 signaling in B cells. Preventing the activation of NF-kappaB by CD40 via a chemical inhibitor of the **IKK complex** (BAY 11-7802) or via inducible **expression** of a dominant negative form of IkappaBalpha significantly reduced the ability of CD40 to increase Pim-1 protein levels. Thus, the regulation of Pim-1 by CD40 is dependent, at least in part, on NF-kappaB activation.

L49 ANSWER 9 OF 17 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

AB pX, the hepatitis B virus-encoded transcription coactivator, is involved in viral infection in vivo. pX stimulates the activity of several transcription factors including nuclear factor-kappaB (NF-kappaB), but the mechanism of activation is poorly understood. The IkappaB kinase complex (IKK) mediates activation of NF-kappaB in response to various

extracellular stimuli, including inflammatory cytokines like tumor necrosis factor and interleukin 1, human T cell lymphoma virus 1 Tax protein, and tumor promoters like phorbol esters. It is not known whether IKK also mediates activation of NF-kappaB by pX. Here we report that IKK was not essential for activation of NF-kappaB by pX. Expression of pX resulted in the degradation of IkappaBalpha in the absence of its phosphorylation at Ser32 and Ser36 residues. Although pX stimulated the activity of cotransfected IKK-beta when it was overexpressed, it failed to activate endogenous IKK. Furthermore, expression of pX stimulated NF-kappaB nuclear translocation and transcriptional activity in IKK-gamma-null fibroblast 5R cells. Our data indicate that pX stimulates NF-kappaB activity through a mechanism that is dependent on IkappaBalpha degradation but not on IKK activation.

L49 ANSWER 10 OF 17 MEDLINE on STN DUPLICATE 8
AB Camptothecin (CPT) and derivatives are topoisomerase I poisons currently used as anticancer drugs. Their cytotoxicity is maximal for cells in S phase. Using asynchronous and S phase-synchronized HeLa cells, we showed that both the nuclear factor-kappaB (NF-kappaB) activation and its transcriptional activity, induced by CPT treatment, are enhanced in S phase cells. After CPT treatment, NF-kappaB activation reached a maximum within 2-3 hr and was still detectable after 24 hr. The nature of the complex evolved with time, forming mostly p50/p65 after 2 hr to almost exclusively p52 after 24 hr. In HeLa cells, the different steps of the induction were readily observable in S phase synchronized cells, whereas they were barely noticeable in a randomly growing cell population. The signal progressed through the activation of the IKK complex, the phosphorylation of IkappaBalpha, and the degradation of phosphorylated-IkappaBalpha and -IkappaBbeta. The stable expression of wild-type HA-tagged-IkappaBalpha or mutated HA-tagged-IkappaBalpha (S32,36A) allowed us to confirm the essential role of Ser32 and Ser36. NF-kappaB-activating kinase (NIK) could play a role upstream of the **IKK complex**, as the transient **expression** of a kinase inactive mutant NIK(K429,430A) abolished the activation of NF-kappaB by CPT. A kinase inactive mutant of mitogen-activated protein/ERK kinase kinase 1 (MEKK1), another kinase susceptible of acting upstream of the signalsome, did not. Cytotoxicity studies with clonal populations expressing different amounts of wild-type or mutated IkappaBalpha revealed that the overexpression of wild-type IkappaBa in large amount increases the sensitivity of HeLa cells to CPT more efficiently than a lower level of expression of non-phosphorylable IkappaBalpha.

L49 ANSWER 11 OF 17 NTIS COPYRIGHT 2004 NTIS on STN
AB In the past 12 months we investigated the ability of IKK to regulate beta-catenin signaling activity. We found that **IKK** exists in a **complex** with beta-catenin and that **expression** of either IKK(alpha) or IKK(beta) can decrease Beta-catenin signaling. However, only a dominant negative (DN) IKK(alpha) mutant increased beta-catenin signaling as well as protein levels. In addition, DN IKK(alpha), but not DN IKK(beta), inhibited the ability of APC to decrease beta- catenin signaling. These results suggest that the IKK proteins are involved in beta-catenin regulation.

L49 ANSWER 12 OF 17 MEDLINE on STN DUPLICATE 9
AB Activation of the transcription factor nuclear factor (NF)-kappaB by proinflammatory stimuli leads to increased expression of genes involved in inflammation. Activation of NF-kappaB requires the activity of an inhibitor of kappaB (IkappaB)-kinase (IKK) complex containing two kinases (IKKalpha and IKKbeta) and the regulatory protein NEMO (NF-kappaB essential modifier). An amino-terminal alpha-helical region of NEMO associated with a carboxyl-terminal segment of IKKalpha and IKKbeta that we term the NEMO-binding domain (NBD). A cell-permeable NBD peptide blocked association of NEMO with the **IKK complex** and

inhibited cytokine-induced NF-kappaB activation and NF-kappaB-dependent gene **expression.** The peptide also ameliorated inflammatory responses in two experimental mouse models of acute inflammation. The NBD provides a target for the development of drugs that would block proinflammatory activation of the IKK complex without inhibiting basal NF-kappaB activity.

L49 ANSWER 13 OF 17 MEDLINE on STN DUPLICATE 10
AB NF-kappa B plays a pivotal role in normal T-cell activation and may also mediate human T-cell leukemia virus (HTLV)-induced T-cell transformation. Activation of NF-kappa B by both T-cell costimulatory signals and the HTLV Tax protein involves stimulation of I kappa B kinase (IKK). As a genetic approach to dissect the intermediate steps involved in NF-kappa B activation in human T cells, we performed somatic cell mutagenesis to isolate signaling-defective mutant Jurkat T-cell lines. One of the mutant cell lines was shown to have a specific blockade in the IKK signaling pathway but remained competent in the c-Jun N-terminal kinase and MAP kinase pathways. Interestingly, this mutant cell line lacks **expression** of IKK gamma, a non-catalytic component of the **IKK complex.** Expression of exogenous IKK gamma in the mutant cells restored NF-kappa B activation by both the T-cell costimulation agents and Tax. These findings provide genetic evidence for the requirement of IKK gamma in NF-kappa B signaling triggered by both T-cell costimulatory signals and HTLV-I Tax protein.

L49 ANSWER 14 OF 17 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 11
AB The interferon (IFN)-inducible double-stranded-RNA (dsRNA)-activated serine-threonine protein kinase (PKR) is a major mediator of the antiviral and antiproliferative activities of IFNs. PKR has been implicated in different stress-induced signaling pathways including dsRNA signaling to nuclear factor kappa B (NF-kappa B). The mechanism by which PKR mediates activation of NF-kappa B is unknown. Here we show that in response to poly(rI) . poly(rC) (pIC), PKR activates I kappa B kinase (IKK), leading to the degradation of the inhibitors I kappa B alpha and I kappa B beta and the concomitant release of NF-kappa B. The results of kinetic studies revealed that pIC induced a slow and prolonged activation of IKK, which was preceded by PKR activation. In PKR null cell Lines, pIC failed to stimulate IKK activity compared to cells from an isogenic background wild type for PKR in accord with the inability of PKR null cells to induce NF-kappa B in response to pIC. Moreover, PKR was required to establish a sustained response to tumor necrosis factor alpha (TNF-alpha) and to potentiate activation of NF-kappa B by cotreatment with TNF-alpha and IFN-gamma. By coimmunoprecipitation, PKR was shown to be physically associated with the **IKK complex.** Transient **expression** of a dominant negative mutant of IKK beta or the NF-kappa B-inducing kinase (NIK) inhibited pIC-induced gene expression from an NP-kappa B-dependent reporter construct. Taken together, these results demonstrate that PKR-dependent dsRNA. induction of NF-kappa B is mediated by NIK and IKK activation.

L49 ANSWER 15 OF 17 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 12
AB Two cytokine-inducible kinases, IKK alpha and IKK beta, are components of a 700-kDa kinase complex that specifically phosphorylates I kappa B. Phosphorylation of I kappa B by IKK leads to its ubiquitination and subsequent degradation, resulting in the nuclear translocation of NF-kappa B. The oncogenic protein Tax, encoded by human T-cell leukemia virus type-1 (HTLV-1), stimulates IKK activity to result in constitutive nuclear levels of NF-kappa B. In an attempt to gain insights into the mechanism by which Tax mediates constitutive activation of the NF-kappa B pathway, we analyzed the chromatographic distribution of IKK proteins using cellular extracts prepared from three T lymphocytes either lacking or containing Tax. IKK kinase activity and the distribution of proteins in the IKK

complex were characterized, In extracts prepared from cells containing Tax, the activity of both IKK alpha and IKK beta present in the 700-kDa **IKK complex** were increased. Surprisingly, cell lines **expressing** Tax also contained an additional peak of IKK beta, but not IKK alpha activity, that migrated at 300 kDa rather than at 700 kDa, We noted that extracts containing Tax had extremely low levels of I kappa B beta, but not I kappa B alpha, and contained predominantly a truncated form of the MAP3K MEKK1. These results suggest that Tax may target several components of the NF-kappa B pathway leading to constitutive activation of this important regulator of cellular gene expression.

L49 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN
AB Colorectal cancer is a major cause of cancer deaths in Western countries, but epidemiol. data suggest that dietary modification might reduce these by as much as 90%. Cyclo-oxygenase 2 (COX2), an inducible isoform of prostaglandin H synthase, which mediates prostaglandin synthesis during inflammation, and which is selectively overexpressed in colon tumors, is thought to play an important role in colon carcinogenesis. Curcumin, a constituent of turmeric, possesses potent anti-inflammatory activity and prevents colon cancer in animal models. However, its mechanism of action is not fully understood. We found that in human colon epithelial cells, curcumin inhibits COX2 induction by the colon tumor promoters, tumor necrosis factor α or fecapentaene-12. Induction of COX2 by inflammatory cytokines or hypoxia-induced oxidative stress can be mediated by nuclear factor kappa B (NF-κB). Since curcumin inhibits NF-κB activation, we examined whether its chemopreventive activity is related to modulation of the signalling pathway which regulates the stability of the NF-κB-sequestering protein, IκB. Recently components of this pathway, NF-κB-inducing kinase and IκB kinases, IKKα and β, which phosphorylate IκB to release NF-κB, have been characterized. Curcumin prevents phosphorylation of IκB by inhibiting the activity of the IKKs. This property, together with a long history of consumption without adverse health effects, makes curcumin an important candidate for consideration in colon cancer prevention.

L49 ANSWER 17 OF 17 MEDLINE on STN DUPLICATE 13
AB NF-kappa B transcription factors play an important role in the activation of the IL-2 gene in response to TCR ligation. The release of NF-kappa B factors to the nucleus requires phosphorylation and degradation of the inhibitory kappa-B proteins (I kappa Bs). I kappa B alpha and I kappa B beta phosphorylation is dependent on dual signaling by the TCR and the CD28 accessory receptor. This pathway involves a multisubunit I kappa B kinase (IKK) complex, which includes the IKK alpha (IKK-1) and IKK beta (IKK-2) kinases. We demonstrate that stimulation of primary human CD4+ T cells by CD3/CD28 activates two distinct endogenous IKK complexes, a heterodimeric IKK alpha/beta and a homodimeric IKK beta complex. IKK beta overexpression in a Jurkat cell line resulted in the formation of a constitutively active IKK complex, which was CD3/CD28 inducible. In contrast, ectopic **expression** of **IKK** alpha assembled into a **complex** with negligible I kappa B kinase activity. Moreover, IKK beta, but not IKK alpha, overexpression enhanced transcriptional activation of the CD28 response element in the IL-2 promoter. Conversely, only kinase-inactive IKK beta interfered in the activation of the IL-2 promoter. Sodium salicylate, an inhibitor of IKK beta, but not IKK alpha, activity, inhibited IL-2 promoter activation as well as IL-2 secretion and interfered in activation of both the heterodimeric as well as the homodimeric IKK complexes in primary CD4+ T cells. Taken together, these data demonstrate the presence of an IKK beta-mediated signaling pathway that is activated by TCR and CD28 coligation and regulates IL-2 promoter activity.

=> log h

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	50.75	52.22

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.70	-0.70

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